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Estimation of Random Effects Models for Repeated Measures

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THESIS

Submitted to the Department of Statistics, Mathematics and Insurance,
Faculty of Commerce, Benha University, in partial Fulfillment
of the Requirements for the Ph.D. in Applied Statistics

2020

Abstract

longitudinal data or repeated measures data arise in many areas as diverse as agriculture, biology, economics, manufacturing, and geophysics. Multivariate nonlinear mixed-effects models (MNLMM) have received increasing use because of their flexibility for analyzing multi-outcome longitudinal data following possibly nonlinear profiles with underlying multivariate normality assumptions for the random effects and within-insubject errors. However, such normality assumption might not offer robust inference if the data, even after being transformed, particularly exhibit skewness.

In our thesis, the researcher proposes a multivariate skew normal-nonlinear mixed model or a multivariate skew normal independent-nonlinear mixed effect models constructed by assuming a multivariate skew normal distribution or a multivariate skew normal independent distribution for the random effects and a multivariate normal distribution or a multivariate normal independent distribution for the random errors. The proposed model is called the multivariate skew normal- nonlinear mixed effects model (MSN-NLMM) and the multivariate skew normal independent- nonlinear mixed-effects model (MSNI-NLMM), allowing for analyzing multi-outcome longitudinal data exhibiting nonlinear growth patterns. To describe the autocorrelation possibly existing among irregularly observed measures, the researcher consider an uncorrelated (UNC) structure, a continuous-type autoregressive model with order1 (AR(1)), and the damped exponential correlation dependence structures for the within-subject errors.

When fitting the MNLMM, it is rather difficult to exactly evaluate the observed log-likelihood function in a closed-form expression, because it involves complicated multiple integrals. To address this issue, the corresponding approximations of the observed log-likelihood function under the three algorithms are proposed. These algorithmic schemes include the penalized nonlinear least squares coupled to the multivariate linear mixed-effects (PNLS-MLME) procedure, Laplacian approximation, the pseudo-data expectation conditional maximization (ECM) algorithm.

We illustrate an efficient expectation conditional maximization algorithm coupled with the first-order Taylor approximation for maximizing the complete pseudo-data likelihood function with real data from HIV/AIDS studies. In light of the criteria which are the maximized log-likelihood ($l_{\max}$), the Akaike information criterion (AIC; Akaike, 1973) and Bayesian information criterion (BIC; Schwarz, 1978) and with UNC, AR(1) and DEC dependence structures for the within-subject errors, the best model is the multivariate skew slash-nonlinear mixed effect models (MSS-NLMM) with DEC dependence. Also, a simulation study is conducted to assess the performance of the proposed models. Bias and mean squared errors are used to evaluate the performance of the estimates via the proposed model. The simulation study shows that the pro-

posed approximate ML estimates based on the EM algorithm provide good asymptotic properties.

To achieve the purpose of this study, the thesis consists of six chapters as follow:

Chapter 1: An introduction includes a background on longitudinal data and mixed effects models in addition to the aims of the study.

Chapter 2: Mixed effects models which discuss both linear and nonlinear mixed effects models.

Chapter 3: Multivariate skew normal nonlinear mixed models in terms of the proposed methods.

Chapter 4: Multivariate skew normal/independent nonlinear mixed models in terms of the proposed methods.

Chapter 5: Application and simulation study : ACTG 315 data.

Chapter 6: Conclusion and future work.